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β_2-Agonists and Doping

A Systematic Review of Randomized Controlled Trials

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Dissertação para a obtenção do Grau de Mestre em
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Resumo

Introdução: A utilização do *doping* no desporto é um problema bastante difundido não apenas entre atletas de elite, mas ainda mais nos desportos recreativos. Os agonistas ß2 podem ser utilizados como doping no desporto, devido às suas ações broncodilatadoras e anti-inflamatórias, mas mais importante ainda pelo seu potencial anabólico. O facto de a sua utilização por parte de atletas estar a aumentar põe em foco se será apenas para tratamento da asma, da asma induzida pelo exercício ou broncoconstrição induzida pelo exercício, ou um uso inadequado por atletas não asmáticos com vista ao benefício dos seus potenciais efeitos ergogénicos.
A "Lista Proibida da Agência Mundial Anti-Doping (WADA) 2019", que lista os fármacos que são considerados ilegais no desporto, postula que todos os agonistas ß2 seletivos e não seletivos, incluindo todos os isómeros óticos, estão proibidos. No entanto, definem-se algumas exceções. Esta proibição é baseada no facto de estes fármacos terem o potencial de melhorar o desempenho físico, o que proporciona uma vantagem competitiva injusta, quando são utilizados por atletas saudáveis.

Objetivos: O objetivo desta dissertação foi, através da realização de uma revisão sistemática baseada em estudos publicados entre 2007 e 2018, avaliar se os agonistas ß2 aumentam o desempenho dos atletas.

Métodos: Uma estratégia de pesquisa sistemática foi conduzida nas bases de dados *Pubmed* e *Science Direct* usando palavras-chave selecionadas previamente (*"adrenergic agonists"* e *"athletic performance"*) entre 2007 e 2018, com o objetivo de identificar estudos aleatorizados e controlados sobre os efeitos dos agonistas ß2 na performance de indivíduos saudáveis. Foi também realizada uma pesquisa manual nas listas de referências de estudos relevantes. Apenas foram selecionados estudos que incluíam indivíduos saudáveis (adultos: homens e mulheres); atletas de elite, atletas recreativos ou indivíduos não atletas. Foram documentados o nível e a intensidade da participação desportiva, o nível de treino (consumo máximo de oxigénio [VO_2max]) e o tipo de desporto dos participantes incluídos. Considerámos qualquer tipo de intervenção com agonistas ß2 de curta ou longa ação, inalados ou sistémicos (administração oral ou intravenosa), cuja administração foi simples (uma administração) ou múltipla (1 ou mais dias até semanas). Foram desenhadas as seguintes análises: atletas versus não atletas; tipo de agonista ß2 (inalado versus sistémico) e duração da intervenção: simples (administração única) versus curta duração (1 semana a ≤6 semanas) ou longa duração (> 6 semanas).

Resultados: Para um mesmo agonista ß2, num indivíduo atleta e num individuo não atleta, foi verificado que em ambos os casos existem efeitos estatisticamente significativos, mas que estes são mais notórios em indivíduos não atletas.
Quando comparados os agonistas ß2 inalados com os agonistas ß2 sistémicos, constatou-se que em ambos os modos de administração do agonista ß2 existem efeitos estatisticamente significativos, efeitos estes que variam de acordo com o agonista ß2 em questão.
Também foi demonstrado um efeito estatisticamente significativo aquando da utilização da combinação de três agonistas ß2 inalados (salbutamol com salmeterol e formoterol).
Relativamente à duração de administração dos agonistas ß2, foi verificado que não há influência numa administração de longa duração, sendo que existem mais efeitos estatisticamente significativos nas administrações únicas.
Quando a análise destes dados é realizada tendo por base as doses permitidas e não permitidas pela WADA, verifica-se que não há efeitos estatisticamente significativos relativamente aos agonistas ß2 nas doses permitidas atualmente pela WADA, e que há efeitos estatisticamente significativos quando usados agonistas ß2 nas doses que nos dias de hoje são proibidas.

Conclusão: Não foram encontrados efeitos estatisticamente significativos relativamente aos agonistas ß2 nas doses permitidas atualmente pela WADA, o que pelo contrário não se verificou nos estudos que incluem agonistas ß2 que nos dias de hoje são proibidos na "Lista Proibida da Agência Mundial Anti-Doping (WADA) 2019". Deste modo, podemos concluir que esta lista deve continuar a ser regularmente atualizada, como tem vindo a ser feito nos últimos anos. Mais estudos sobre estes e outros fármacos, que possam potenciar a performance atlética, devem ser realizados, tentando envolver um maior número de participantes, indivíduos atletas e não atletas, doses maiores e simular a utilização destes em contexto de competição.

Palavras-chave: Agonistas ß2; desempenho; *doping*; atletas; desporto.

Abstract

Background: Doping in sport is a widespread problem not just among elite athletes, but mainly in recreational sports. ß2-agonists may be used for doping in sport because of their bronchodilator and anti-inflammatory actions, but more importantly for their potential anabolic action. The question of whether their use has increased due to asthma, EIA or EIC, or due to a misuse by non-asthmatic athletes because of potential ergogenic effects, remains open. The ‘‘Prohibited List of the World Anti-Doping Agency (WADA) 2019”, which lists the drugs that are considered illegal in sports, states that all selective and non-selective ß2-agonists, including all optical isomers, are prohibited. However, there are some exceptions. This prohibition is based on the fact that these drugs have the potential to improve physical performance, which leads to an unfair competitive advantage when taken by healthy athletes.

Objectives: The aim of this dissertation was to conduct a systematic review to evaluate if ß2-agonists do indeed increase athletes’ performance, based on published studies between 2007 and 2018.

Methods: A systematic search strategy was conducted in *Pubmed* and *Science Direct* using selected keywords (“adrenergic agonists” and “athletic performance”) between 2007 and 2018. A manual search of the reference lists of relevant articles was also undertaken in this review.

Results: When comparing the results for the same ß2-agonists on an athlete and on a non-athlete person we can verify that in both cases, there are statistically significant effects, but they are more prominent on non-athlete individuals.
When comparing the inhaled ß2-agonists with the systemic ß2-agonists, we found out that there are statistically significant effects in both administration modes, but these effects vary according with the administrated ß2-agonist.
We found out, as well, a statistically significant effect when an inhaled combination of salbutamol with salmeterol and formoterol was studied.
Regarding the duration of the administration, we verified no influence on a longer administration since there are more statistically significant effects on single administrations.
When these data were analysed based on the doses permitted and forbidden by WADA, we could verify that there were not statistically significant effects regarding ß2-agonists on the permitted doses by WADA, and that there were statistically significant effects when ß2-agonists were used on the doses nowadays.

Conclusion: There were not found statistically significant effects regarding ß2-agonists on the permitted doses by WADA, which in contrast was not verified on the studies that include ß2-agonists nowadays forbidden by the "Prohibited List of the World Anti-Doping Agency (WADA) 2019". Being so, we could conclude that this list should be continuously updated as it has been done lately.

Key-words: ß2-agonists; performance; doping; athletes; sport.

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List of Acronyms

WADA: World Anti-Doping Agency

EIA: exercise-induced asthma

EIC: exercise-induced bronchoconstriction

AHR: airway hyperreactivity

TUE: Therapeutic Use Exemption

AAF: Adverse Analytical Finding

VO_2max: maximal oxygen consumption

SD: standard deviation

F: female

M: male

Wk: week

PP: peak power

MP: mean power

FI: fatigue index

TTE: time to exhaustion

TT: time trial

CPT: concentric peak torque

ST: sprint time

MVC: maximal voluntary isometric contraction

TPP: time to peak power

MIMS: maximal isokinetic muscle strength

HR: heart rate

SBP: systolic blood pressure

DBP: diastolic blood pressure

Ve: expiratory volume

MSNA: muscle sympathetic nerve activity

vmax: maximal velocity

Fmax: maximal force

Pmax: maximal power output

vopt: optimal velocity

Fopt: optimal force

vmean: mean velocity

vmax/τ: initial acceleration

RM: repetition maximum

EP: end power

1. Introduction

Doping in sport is a widespread problem not just among elite athletes, but mainly in recreational sports. ß2-agonists may be used for doping in sport because of their bronchodilator and anti-inflammatory actions, but more importantly for their potential anabolic actions. (1)

It is known that athletes mainly use ß2-agonists for the treatment of asthma, exercise-induced asthma (EIA) and exercise-induced bronchoconstriction (EIC); diseases that could affect their performance on competitions.

Asthma is defined as a chronic inflammatory disorder of the airways with bronchial hyperresponsiveness and variable bronchoconstriction. (2)

EIA and EIC describe two clinical entities where exercise triggers bronchial hyperresponsiveness. Exercise is a common trigger for bronchospasm in the asthmatic (EIA), as well as in athletes without the underlying inflammation associated with asthma (EIC).

EIA historically describes those with a history of asthma who exhibit a bronchospastic response during or after an exercise bout, while those athletes with EIC do not have a history of asthma and experience no symptoms outside of workout. Although both entities commonly share airway hyperreactivity (AHR), they should be clinically categorized as two distinct entities: testing for and treatment of each one may be uniquely different. (3)

Inhaled ß2-agonists are essential in the management of asthma, EIA in asthmatic athletes and EIC, allowing these athletes to train and compete at the highest level of performance. (4) However, it was noted since 1984 that the percentage of athletes using inhaled ß2-agonists at the Olympic Games had slightly risen. The question of whether this is a real increase because of asthma, EIA or EIC, or a misuse by non-asthmatic athletes because of potential ergogenic effects remains open. The increase in the use of inhaled ß2-agonists has led to more stringent anti-doping rules regarding these substances (2) and since 2001, asthmatic athletes must provide clinical evidence of reversible airway obstruction or bronchial responsiveness in order to use ß2-agonists legitimately (4).

The starting point of these rules can be traced back to 1972 when inhaled salbutamol was prohibited for the first time at the Olympic Games. Since then, inhaled ß2-agonists have alternately been allowed and prohibited. (5)

The ‘‘Prohibited List of the World Anti-Doping Agency (WADA) 2019”, which lists the drugs that are considered illegal in sports, states that all selective and non-selective ß2-agonists, including all optical isomers, are prohibited. Including, but not limited to:

- Fenoterol;
- Formoterol;
- Higenamine;
- Indacaterol;

- Olodaterol;
- Procaterol;
- Reproterol;
- Salbutamol;
- Salmeterol;
- Terbutaline;
- Tretoquinol (trimetoquinol);
- Tulobuterol;
- Vilanterol.

There are, however, some exceptions:

- Inhaled salbutamol: maximum 1600 micrograms over 24 hours in divided doses not to exceed 800 micrograms over 12 hours starting from any dose;
- Inhaled formoterol: maximum delivered dose of 54 micrograms over 24 hours;
- Inhaled salmeterol: maximum 200 micrograms over 24 hours. (6)

These exceptions are allowed if an athlete has an illness whose treatment requires him or her to take a medicine or use a method that falls under the Prohibited List. In these cases the athlete may apply for a Therapeutic Use Exemption (TUE) which may give him or her the authorisation to take the prohibited medicine or use the prohibited method for the treatment of the illness. (7)

The presence in the urine of salbutamol in excess of 1000 ng/mL or formoterol in excess of 40 ng/mL is not consistent with therapeutic use of the substance and will be considered as an Adverse Analytical Finding (AAF) unless the athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of a therapeutic dose (by inhalation) up to the maximum dose indicated above. (6)

This prohibition is based on the assumption that these drugs have the potential to improve physical performance which leads to an unfair competitive advantage when taken by healthy athletes.

Despite the suspicions, the certainty that there is even an increase in performance and, if it exists, how this increase occurs is still not well understood. The discrepancies between inhaled and oral administration of ß2-agonists on performance are commonly believed to be a consequence of the route of administration. (8) Therefore, we have done a systematic review with the aim of evaluating if ß2-agonists do indeed increase athletes' performance.

2. Literature Search Methodology

2.1 Criteria for Considering Studies for this Review

2.1.1 Types of Studies

We considered all randomized, double blind, crossover controlled studies that reported the effect of ß2-agonists on physical performance published between 2007 and 2018.

2.1.2 Types of Participants

We only included studies with healthy subjects (adults, male and female). We search for studies on elite athletes, recreational athletes and non-athletic people. We tried to document the level and intensity of sports participation, the training level (maximal oxygen consumption [VO_2max]) and the type of sport at inclusion. Athletes were considered to be highly trained if they had a VO_2max above 55 mL/kg/min (females) or 60 mL/kg/min (males).
We excluded studies that included participants with any kind of disease, such as asthma, chronic obstructive pulmonary disease or cardiovascular diseases; as well as studies in which participants used other medication (except oral contraception in women), unless the results of healthy subjects were presented separately.

2.1.3 Types of Interventions

We considered any intervention with short or long-acting inhaled or systemic (oral or intravenous) ß2-agonist, whose use was single (once) or multiple administrations (1 or more days to weeks).
We excluded studies that included clenbuterol, because this drug is defined as an anabolic agent and not a ß2-agonist by the WADA. (6)

2.1.4 Types of Outcome Measures

The types of outcome measures in the studies were as follows:

1. VO_2max in L/min or mL/Kg/min determined with a maximal exercise test on a treadmill or cycle ergometer.
2. Endurance time(s) to exhaustion during an exercise test at a predetermined percentage of VO_2max.
3. Mean power (W) and duration time (s) of a time trial; cycling economy (W/L of O_2), in which a certain distance had to be covered or a certain amount of work had to be delivered.
4. Peak power (W or W/kg); mean power (W); force (N or N/kg); velocity (rpm); time to peak power (s) and fatigue index (%) during a Wingate test.

5. Maximal voluntary isometric contraction of muscles (N); the one-repetition maximum (1RM, kg) or concentric peak torque (Nm/s or Nm/kg/s) during an isokinetic strength test of any muscle group.
6. Maximal isokinetic muscle strength (N); Isometric Handgrip [Heart rate (bpm); Systolic Blood Pressure (mmHg); Diastolic Blood Pressure (mmHg); Pulse Pressure (mmHg); Expiratory volume (L/min); $P_{ET}CO_2$; Muscle sympathetic nerve activity (burst/min)].

2.2 Search Methods for Identification of Studies

We undertook a systematic search of two electronic databases PUBMED (from 2007 to 2018) and SCIENCE DIRECT (from 2007 to 2018) to identify randomized controlled trials about the effects of ß2-agonists on healthy humans' performance. On that search we applied some filters to refine it as well as the combination of MeSH terms "adrenergic agonists" and "athletic performance". To guarantee we collected as much information as possible we also undertook a manual search of the reference lists of relevant articles.

This systematic literature review was registered in the PROSPERO International Prospective Register of Systematic Reviews - *CRD42018112905 Beta-2 adrenergic agonists and physical performance* - and was performed according to the recommendations established by the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement guidelines.

2.3 Data Collection and Analysis

2.3.1 Selection of Studies

After downloading all the studies, duplicates were removed, and all titles and abstracts were analysed systematically. During this step, most of the studies were eliminated. Those studies considered relevant were read in full to enforce the inclusion and exclusion criteria. The PRISMA diagram shown in figure 1 summarizes the steps of article selection and the characteristics of excluded studies.

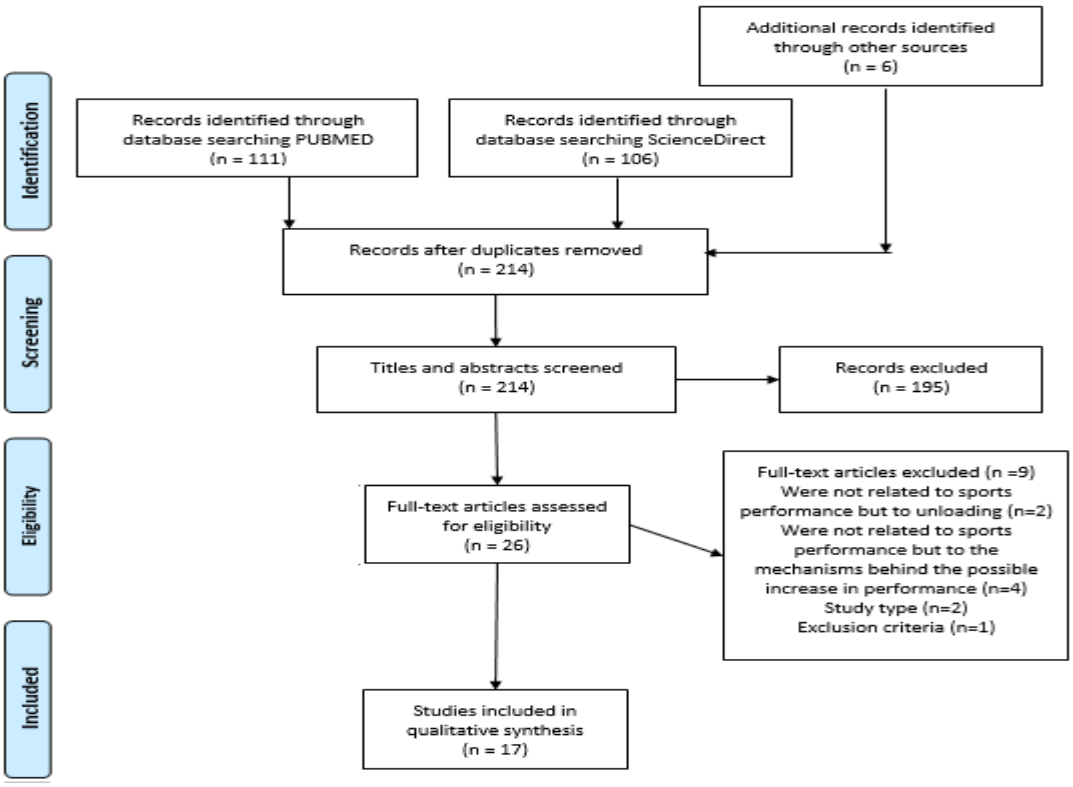

Figure 1 - PRISMA 2009 flow diagram for search results.

2.3.2 Data Extraction and Management

From each study the following information was extracted: authors; year of study; design; participants (sample size, sex, age [mean ± SD]; type and level of sports' participation; training level (VO_2max); intervention (drugs' type, dose, study duration) and outcome (type of outcome analysis, outcomes analysed).

2.3.3 Assessment of Risk of Bias in Included Studies

The risk of bias of each study was independently assessed by two reviewers (R. V. and O.L.) using the methodological criteria "Cochrane collaboration's tool for assessing risk of bias". In addition to the specific domains recommended for Cochrane reviews, we added if participants were adequately tested for asthma. We scored each item with "Y" (YES), "N" (NO) or "?" (UNCLEAR). A consensus method was used to resolve disagreements.

2.3.4 Data Analysis

We designed the following analyses: athletes versus non-athletes; type of ß2-agonists (inhaled versus systemic) and duration of the intervention: single (once) versus short term (1 week to ≤6 weeks) or long term (> 6 weeks).

3. Findings

3.1 Search Results

The search was carried out between July and October 2018 and 223 studies were identified, 217 on the databases and 6 through a manual search on the reference lists of relevant articles (figure 1). Out of the total 223 records, 9 were removed because they were duplicated, so we read 214 titles and abstracts for possible eligibility. 26 records were read in full-text and 9 were excluded: not related to sports performance but to unloading (n=2); not related to sports performance but to the mechanisms behind the possible increase in performance (n=4); study type (n=2); exclusion criteria (n=1). In the end, only 17 studies were included in this analysis.

3.2 Description of Studies

The characteristics of the included studies are shown in table 1.

Thirteen studies involving 269 participants compared inhaled ß2-agonists with placebo. (4,8–19) Twelve of these thirteen studies were single treatment and the other one lasted 6 weeks (short-term treatment). (17) Eight studies involved athletes. (4,9,10,12,14–16,20) One study involved an inhaled combination of salbutamol with salmeterol and formoterol. (15)

Four studies involving 62 participants compared systemic ß2-agonists with placebo. (20–23) Two studies investigated the effect of the use of oral salbutamol (20,21) and one study investigated the effect of the use of oral terbutaline (23). One study with 23 participants compared intravenous salbutamol with placebo. (22) Only one of these studies involved athletes. (20) Tree studies were single treatment (21–23) and the other one lasted 2 weeks (short-term treatment) (20).

Table 1 - Characteristics of the included studies.

Study, year	Design	Study population		Intervention	Primary outcome measures
		no. of subjects; sex; age [y] ± SD	activity and performance level		
Tjorhom et al., (4) 2007	Crossover	23; M; 29.2 ± 4.5	Endurance athletes; VO_2max 4.8 ± 0.29 L/min	Formoterol 18 µg inhaled	Running time to exhaustion at -20°C at 107% VO_2max
Le Panse et al., (21) 2007	Crossover	12; F; 22.3 ± 0.9	Athletics, weightlifting, basketball; 1-3 times per wk	Salbutamol 4 mg oral	30 s Wingate test protocol
Sporer et al., (12) 2007	4-way Crossover	30; M; 29 ± 6	Cyclists, triathletes; VO_2max 67.1 ± 4.3 mL/kg/min	Salbutamol 200 µg; 400 µg; 800 µg inhaled	Mean power and duration of 20 km time
Decorte et al., (13) 2008	3-way Crossover	10; M; 23.3 ± 3.2	Physically active; 5.9 ± 2.0 h/wk	Salbutamol 200 µg; 800 µg inhaled	Quadriceps muscle strength during maximal voluntary contraction and femoral nerve magnetic stimulation before and after (i) a maximal incremental cycling test and (ii) 50 maximal isometric one-leg extensions
Beloka et al., (22) 2011	3-way Crossover	23; M; 23 ± 2.3	Physically active	Salbutamol 10 µg/min; 20 µg/min IV	Muscle sympathetic nerve activity; peripheral and central chemosensitivity; metabosensitivity; cardiopulmonary exercise test; isokinetic muscle strength
Sanchez et al., (23) 2012	Crossover	7; M; 29 ± 6	Competitive athletes; 10h/wk; VO_2max 57 ± 3 mL/kg/min	Terbutaline 8 mg oral	Force-velocity exercise test; running sprint; maximal endurance cycling test
Decorte et al., (14) 2013	3-way Crossover	11; M; 33 ± 6	Highly trained: cyclists, triathletes; runners; 12 ± 3 h/wk; VO_2max ≥ 65 mL/kg/min	Salbutamol 200 µg; 800 µg inhaled	Quadriceps fatigue test [concentric peak torque (Nm/s)]
Kalsen et al., (15) 2013	Crossover	13(M) 4(F); 17.9 ± 0.9	Elite swimmers; VO_2max 3940 ± 165 mL/min	Salbutamol (8x200 µg); Salmeterol (4x50 µg); Formoterol (4x9 µg) (combined inhalation)	Maximal voluntary isometric contraction of m. quadriceps; swim ergometer sprint time; exhaustive swim test (Time To Exhaustion)
Koch et al., (16) 2013	Crossover	35; M; 29 ± 5	Cyclists, triathletes; VO_2max 65.7 ± 6.7 mL/kg/min	Salbutamol 400 µg inhaled	Mean power during the 10 km time trial cycle ergometer
Dickinson	Mixed-	16; M; 20.1 ± 1.6	Amateur-level competition	Salbutamol 1600 µg	Peak oxygen consumption; duration of 3 km

et al., (17) 2013	model repeated measures		(soccer; running; cycling; gaelic football; boxing; kick boxing; rugby; gymnastics; tennis)	inhaled, during 6 weeks	time trial; vertical jump height; 1 repetition maximum bench and leg press; peak torque knee flexion and extension
Hostrup et al., (20) 2014	Parallel study	20; M; 25.9 ± 1.8	Elite endurance athletes (cycling; mountain biking; triathlon); 14.9 ± 1 h/wk; VO_2max 69.4 ± 1.8 mL/kg/min	Salbutamol 4 mg oral acute administration + after 2 wk administration	30 s Wingate test protocol (PP; MP; FI); maximal voluntary isometric contraction of m. quadriceps; isometric endurance (TTE during isometric contraction of m. deltoideus); exercise performance at 110% of VO_2max (TTE)
Koch et al., (18) 2014	Crossover	15; F	Athletes; VO_2max ≥ 50 mL/kg/min	Salbutamol 400 µg inhaled	Mean power; oxygen consumption and cycling economy on a 10 km time trial on a cycle ergometer
Hostrup et al., (8) 2014	Crossover	9; M; 24.3 ± 1.1	Recreational athletes (Cycling; Running; Resistance training); 10.2 ± 1.2 h/wk; VO_2max 58.9 ± 3.1 mL/kg/min	Terbutaline 30x0.5 mg inhaled	Maximal voluntary isometric contraction of m. quadriceps; 30 s Wingate test protocol; time trial performance 100 kcal
Kalsen et al., (19) 2014	Crossover	9; M; 24.3 ± 1.1	Moderately trained; VO_2max 58.7 ± 3.1 mL/kg/min	Terbutaline 15 mg inhaled	Time trial performance 300 kcal
Koch et al., (9) 2014	Mixed-model repeated measures	69; M + F	Cyclists; VO_2max 62.3 ± 7.6 mL/kg/min	Salbutamol 400 µg inhaled	Mean power output and duration of 10 km time trial
Koch et al., (10) 2015	Crossover	12; M; 31 ± 7	Trained competitive (Cyclists and triathletes); VO_2max 64.8 ± 6 mL/kg/min	Salbutamol 1600 µg inhaled	Mean duration of the 10 km cycling time trial
Kalsen et al., (11) 2016	Crossover	13; M; 32 ± 2	Recreational active subjects; 1.8 ± 0.3 h/wk; VO_2max 45 ± 0.2 mL/kg/min	Formoterol 54 µg inhaled	Power output; maximal voluntary contraction of m. quadriceps; 30s cycle ergometer sprint
SD = standard deviation; **F** = female; **M** = male; $\boldsymbol{VO_2max}$ = maximal oxygen consumption; **wk** = week; **PP** = peak power; **MP** = mean power; **FI** = fatigue index; **TTE** = time to exhaustion					

3.3 Assessment of the Risk of Bias

The results of the risk of bias assessment in individual studies are shown in table 2.

All the studies using inhaled ß2-agonists (fourteen) had adequate allocation concealment, whereas the sequence generation was described in only six of the fourteen studies. However, this is unlikely to have been a source of bias because all the studies (14/14) were double blinded. In eight studies the participants were adequately tested for asthma. In six of the fourteen studies, masking of treatment characteristics was incomplete, due to the side effects felt by the participants who took the drugs.

Only one of the four studies using systemic ß2-agonists had no adequate allocation concealment and no adequate sequence generation, which means this is unlikely to have been a source of bias because all studies (4/4) were double blind. Only in 2 of 4 studies the participants were adequately tested for asthma. In three of the four studies, the masking of treatment characteristics was incomplete due to the side effects felt by the participants who take the drugs.

3.4 Effect of Interventions

3.4.1 Athletes

Eight studies involving 217 participants addressed the effects of ß2-agonists on athletes. The summary results are presented on table 3.

A statistically significant effect was detected for inhaled salbutamol 200 µg/800 µg (14); inhaled combination of salbutamol (8x200 µg) with salmeterol (4x50 µg) and formoterol (4x9 µg) (maximal voluntary contraction and swim ergometer sprint time) (15); oral salbutamol 4 mg acute administration and two weeks administration (peak power) (20).

The effect estimates for inhaled formoterol 18 µg (4); inhaled salbutamol 200 µg/400 µg/800 µg (12); inhaled salbutamol 400 µg (9,16) and inhaled salbutamol 1600 µg (10) were negative (not statistically significant).

3.4.2 Non-athletes

Nine studies involving 114 participants addressed the effects of ß2-agonists on non-athletes. The summary results are presented on table 4.

A statistically significant effect was detected for oral salbutamol 4 mg (21); intravenous salbutamol 10 µg/min and intravenous salbutamol 20 µg/min (22); oral terbutaline 8 mg (Fmax) (23); inhaled salbutamol 400 µg (VO_2max) (18); inhaled terbutaline 30x0.5 mg (8) and inhaled formoterol 54 µg (11).

The effect estimates for inhaled salbutamol 200 µg (13); inhaled salbutamol 800 µg (13); inhaled salbutamol 1600 µg (during 6 weeks) (17); inhaled terbutaline 15 mg (19) were negative (not statistically significant).

Table 2 - Risk of bias assessment for the included studies.

Study, year	Adequate sequence generation	Allocation concealment	Blinding of participants	Blinding of researchers	Blinding of outcome assessors	Incomplete outcome data addressed (withdrawals)	Were the participants adequately tested for asthma?	Total number of fulfilled anti-bias criteria
Tjorhom et al., (4) 2007	Y	Y	Y	Y	Y	Y	Y	7
Le Panse et al., (21) 2007	?	?	Y	Y	?	?	?	2
Sporer et al., (12) 2007	?	Y	Y	Y	?	Y	Y	5
Decorte et al., (13) 2008	?	Y	Y	Y	Y	N	N	4
Beloka et al., (22) 2011	Y	Y	Y	Y	?	N	N	4
Sanchez et al., (23) 2012	Y	Y	Y	Y	?	N	Y	5
Decorte et al., (14) 2013	?	Y	Y	Y	?	N	N	3
Kalsen et al., (15) 2013	?	Y	Y	Y	?	N	Y	4
Koch et al., (16) 2013	Y	Y	Y	Y	?	Y	Y	6
Dickinson et al., (17) 2013	Y	Y	Y	Y	Y	N	Y	6
Hostrup et al., (20) 2014	Y	Y	Y	Y	?	N	Y	5
Koch et al., (18)	Y	Y	Y	Y	?	Y	Y	6

2014								
Hostrup et al., (8) 2014	Y	Y	Y	Y	?	Y	N	5
Kalsen et al., (19) 2014	?	Y	Y	Y	?	N	N	3
Koch et al., (9) 2014	Y	Y	Y	Y	N	Y	Y	6
Koch et al., (10) 2015	?	Y	Y	Y	?	Y	Y	5
Kalsen et al., (11) 2016	?	Y	Y	Y	Y	Y	N	5
Y = YES; **N** = NO; **"?"** indicates UNCLEAR								

Table 3 - Effect of the interventions on athletes.

Study, year	Primary outcome measures	No of participants	Type, dose, duration of ß2-agonists	Results ß2-agonists	Results Placebo	Conclusion
Tjorhom et al., (4) 2007	Running time to exhaustion at -20°C at 107% VO_2max	23	Formoterol 18 µg inhaled	Running time = 274 (246-307) s	Running time = 270 (242-298) s	No changes
Sporer et al., (12) 2007	Mean power and duration of 20 km time trial	30	Salbutamol 200 µg; 400 µg; 800 µg inhaled	Mean power = 306 - 310 W	Mean power = 306 - 310 W	No changes
				TT = 30.56 ± 1.03 (200 µg) vs 30.67 ± 1.06 (400 µg) vs 30.70 ± 1.04 (800 µg) min	TT = 30.72 ± 1.06 min	No changes
Decorte et al., (14) 2013	Quadriceps fatigue test	11	Salbutamol 200 µg; 800 µg inhaled	CPT = 78 ± 8 (200 µg) vs 82 ± 7 (800 µg) Nm/s	CPT = 72 ± 7 Nm/s	Increase
Kalsen et al., (15) 2013	Maximal voluntary isometric contraction of m. quadriceps; swim ergometer sprint time; exhaustive swim test (Time To Exhaustion)	17	Salbutamol (8x200 µg); Salmeterol (4x50 µg); Formoterol (4x9 µg) (combined inhalation)	MVC increase with 6 ± 1 % after inhalation of ß2-agonists		Increase
				ST = 58.3 ± 1 s	ST = 57.4 ± 1.1 s	Increase
				TTE = 187 ± 38 s	TTE = 147 ± 20 s	No changes
Koch et al., (16) 2013	Mean power during the 10 km time trial cycle ergometer	35	Salbutamol 400 µg inhaled	Mean power = 4.07 ± 0.47 W	Mean power = 4.04 ± 0.38 W	No changes
Hostrup et al., (20) 2014	30 s Wingate test protocol (PP; MP; FI); Maximal voluntary isometric contraction of m. quadriceps; Isometric endurance (TTE during isometric contraction of m. deltoideus); Exercise performance at 110% of VO_2max (TTE)	20	Salbutamol 4 mg oral acute administration	PP increase during the first bout by 4.1 ± 1.7 %		Increase
				MP (1; 2; 3 bouts) = 695 ± 11 W; 632 ± 10 W; 602 ± 9 W	MP (1; 2; 3 bouts) = 672 ± 17 W; 614 ± 16 W; 574 ± 16 W	No changes
				FI (1; 2; 3 bouts) = 40 ± 2 %; 44 ± 2 %; 46 ± 1 %	FI (1; 2; 3 bouts) = 41 ± 3 %; 48 ± 3 %; 50 ± 3 %	No changes
				MVC = 650-700 N	MVC = 650-700 N	No changes
				TTE m. deltoideus = 120 ± 8 s	TTE m. deltoideus = 125 ± 10 s	No changes
				TTE a $VO_2máx$ 110% = 225 ± 23 s	TTE a $VO_2máx$ 110% = 197 ± 17 s	No changes

			Salbutamol 4 mg oral after 2wk administration	PP increase during the first bout by 6.4 ± 2.0 % and the second bout by 4.2 ± 1.0 %		Increase
				MP (1; 2; 3 bouts) = 690 ± 13 W; 630 ± 11 W; 601 ± 12 W	MP (1; 2; 3 bouts) = 669 ± 16 W; 609 ± 15 W; 570 ± 15 W	No changes
				FI (1; 2; 3 bouts) = 40 ± 2 %; 47 ± 2 %; 48 ± 2 %	FI (1; 2; 3 bouts) = 43 ± 3 %; 49 ± 4 %; 48 ± 3 %	No changes
				MVC = 650-700 N	MVC = 650-700 N	No changes
				TTE m. deltoideus = 118 ± 8 s	TTE m. deltoideus = 129 ± 8 s	No changes
				TTE a $VO_2máx$ 110% = 233 ± 24 s	TTE a $VO_2máx$ 110% = 202 ± 23 s	No changes
Koch et al., (9) 2014	Mean power output during a 10 km time trial	69	Salbutamol 400 µg inhaled	Mean power output = 3.6 - 4.2 W	Mean power output = 3.6 - 4.3 W	No changes
Koch et al., (10) 2015	Mean duration of the 10 km cycling time trial	12	Salbutamol 1600 µg inhaled	Mean duration = 15 min 34 s	Mean duration = 15 min 39 s	No changes
TT = time trial; **CPT** = concentric peak torque; **ST** = sprint time; **TTE** = time to exhaustion; **MVC** = maximal voluntary isometric contraction; **PP** = peak power; **MP** = mean power; **FI** = fatigue index						

Table 4 - Effect of the interventions on non-athletes.

Study, year	Primary outcome measures	No of participants	Type, dose, duration of ß2-agonists	Results ß2-agonists	Results Placebo	Conclusion
Le Panse et al., (21) 2007	30 s Wingate test protocol	12	Salbutamol 4 mg oral	PP = 778.8 (44.0) W	PP = 732.9 (39.9) W	Increase
				PP = 13.2 (0.6) W/kg	PP = 12.6 (39.9) W/kg	Increase
				MP = 414.4 (17.4) W	MP = 395.7 (15.8) W	Increase
				Force (PP) = 65.2 (3.4) N	Force (PP) = 57.6 (3.2) N	Increase
				Force (PP) = 1.12 (0.06) N/Kg	Force (PP) = 0.98 (0.03) N/Kg	Increase
				Velocity (PP) = 121.0 (4.2) rpm	Velocity (PP) = 129.2 (6.3) rpm	No changes
				TPP = 1.79 (0.08) s	TPP = 2.65 (0.17) s	Increase
				FI = 66.6 (1.7) %	FI = 63.5 (2.0) %	No changes
Decorte et al., (13) 2008	Quadriceps muscle strength during maximal voluntary contraction and femoral nerve magnetic stimulation (TwQpeak) after (i) a maximal incremental cycling test and (ii) 50 maximal isometric one-leg extensions	10	Salbutamol 200 µg inhaled	before and after (i)		
				MVC before = 638.0 ± 117.2 N	MVC before = 649.9 ± 138.1 N	No changes
				TwQpeak before = 240.0 ± 82.0 N	TwQpeak before = 241.5 ± 86.2 N	No changes
				MVC after = 592.7 ± 113.9 N	MVC after = 554.1 ± 114.3 N	No changes
				TwQpeak after = 196.0 ± 54.3 N	TwQpeak after = 181.6 ± 69.1 N	No changes
				before and after (ii)		
				MVC before = 603.6 ± 162.8 N	MVC before = 539.6 ± 131.3 N	No changes
				TwQpeak before = 209.0 ± 62.6 N	TwQpeak before = 186.0 ± 92.2 N	No changes
				MVC after = 536.2 ± 129.0 N	MVC after = 486.5 ± 119.1 N	No changes
				TwQpeak after = 153.9 ± 77.7 N	TwQpeak after = 133.2 ± 78.1 N	No changes
			Salbutamol 800 µg	before and after (i)		

			inhaled	MVC before = 642.1 ± 119.3 N	MVC before = 649.9 ± 138.1 N	No changes
				TwQpeak before = 259.8 ± 98.9 N	TwQpeak before = 241.5 ± 86.2 N	No changes
				MVC after = 595.5 ± 92.9 N	MVC after = 554.1 ± 114.3 N	No changes
				TwQpeak after = 235.4 ± 84.8 N	TwQpeak after = 181.6 ± 69.1 N	No changes
				before and after (ii)		
				MVC before = 565.7 ± 152.0 N	MVC before = 539.6 ± 131.3 N	No changes
				TwQpeak before = 232.9 ± 71.3 N	TwQpeak before = 186.0 ± 92.2 N	No changes
				MVC after = 505.3 ± 102.9 N	MVC after = 486.5 ± 119.1 N	No changes
				TwQpeak after = 167.7 ± 57.3 N	TwQpeak after = 133.2 ± 78.1 N	No changes
Beloka et al., (22) 2011	Maximal isokinetic muscle strength; Isometric Handgrip (Heart rate; Systolic Blood Pressure; Diastolic Blood Pressure; Pulse Pressure; expiratory volume; $P_{ET}CO_2$; Muscle sympathetic nerve activity)	23	Salbutamol 10 µg/min IV	MIMS	MIMS	No changes
				HR = 71 ± 10 bpm	HR = 67 ± 7 bpm	Increase
				SBP = 122 ± 12 mm Hg	SBP = 111 ± 15 mm Hg	Increase
				DBP = 66 ± 7 mm Hg	DBP = 66 ± 10 mm Hg	No changes
				Pulse Pressure = 46 ± 6 mm Hg	Pulse Pressure = 52 ± 6 mm Hg	Decrease
				Ve = 8.6 ± 1.1 L/min	Ve = 7.6 ± 1.5 L/min	Increase
				$P_{ET}CO_2$ = 40 ± 5	$P_{ET}CO_2$ = 38 ± 5	No changes
				MSNA = 18 ± 5 (burst/min)	MSNA = 20 ± 10 (burst/min)	No changes
			Salbutamol 20 µg/min IV	MIMS	MIMS	No changes
				HR = 112 ± 12 bpm	HR = 67 ± 9 bpm	Increase
				SBP = 138 ± 14 mm Hg	SBP = 125 ± 7 mm Hg	Increase
				DBP = 64 ± 8 mm Hg	DBP = 72 ± 5 mm Hg	Decrease
				Pulse Pressure = 53 ± 6 mm Hg	Pulse Pressure = 75 ± 9 mm Hg	Decrease
				Ve = 9.5 ± 1.9 L/min	Ve = 7.7 ± 1.3 L/min	Increase

				$P_{ET}CO_2$ = 43 ± 5	$P_{ET}CO_2$ = 44 ± 3	No changes
Sanchez et al., (23) 2012	Force-velocity exercise test (vmax; Fmax; Pmax; vopt; Fopt); Running sprint (vmax; vmean; vmax/τ); Maximal endurance cycling test (Peak O_2 uptake; Peak ventilation; TTE)	7	Terbutaline 8 mg oral	vmax = 190 (17) rpm	vmax = 183 (8) rpm	No changes
				Fmax = 231.1 (38.2) N	Fmax = 245.4 (36.9) N	Increase
				Pmax = 24.7 (2.3) W/Kg	Pmax = 25.8 (3.3) W/Kg	No changes
				vopt = 101.8 (8.9) rpm	vopt = 100.1 (7.2) rpm	No changes
				Fopt = 141.9 (31.1) N	Fopt = 150.2 (34.2) N	No changes
				vmax = 8.4 (0.5) m/s	vmax = 8.6 (0.4) m/s	No changes
				vmean = 6.3 (1.1) m/s	vmean = 6.2 (1.3) m/s	No changes
				vmax/τ = 5.0 (0.6) m/s	vmax/τ = 5.1 (1.7) m/s	No changes
				Peak O_2 uptake = 53.3 (3.8) ml/Kg/min	Peak O_2 uptake = 51.7 (3.3) ml/Kg/min	No changes
				Peak ventilation = 109.3 (20.2) L/min	Peak ventilation = 114.1 (13.3) L/min	No changes
				TTE = 845 (736) s	TTE = 714 (392) s	No changes
Dickinson et al., (17) 2013	Peak oxygen consumption (VO_2 peak); duration of 3 km time trial; vertical jump height; 1 repetition maximum bench and leg press; peak torque knee flexion and extension	16	Salbutamol 1600 µg inhaled, during 6 weeks	VO_2 peak = 4.0 - 4.4 L/min	VO_2 peak = 4.0 - 4.4 L/min	No changes
				Duration 3 km TT = 900 - 1100 s	Duration 3 km TT = 900 - 1100 s	No changes
				Vertical Jump Height = 50-55 cm	Vertical Jump Height = 50-55 cm	No changes
				1 RM bench press = 70 - 75 kg	1 RM bench press = 70 - 75 kg	No changes
				1 RM leg press = 270 - 290 kg	1 RM leg press = 270 - 290 kg	No changes
				Peak torque = 60 - 150 N.m	Peak torque = 60 - 200 N.m	No changes
Koch et al., (18) 2014	Mean power; Oxygen Consumption (VO_2max); Cycling economy on a 10 km time trial on a cycle ergometer	15	Salbutamol 400 µg inhaled	Mean power = 207 (20) W	Mean power = 210 (15) W	Decrease
				VO_2max = 47.8 (6.0) mL/kg/min	VO_2max = 45.9 (3.6) mL/kg/min	Increase
				Economy = 72.9 (6.8) W/L/min	Economy = 75.5 (4.1) W/L/min	Decrease
Hostrup et al., (8)	Maximal voluntary	9	Terbutaline 30x0.5	MVC increase by 8.4 ± 3.0 % with		Increase

2014	isometric contraction of m. quadriceps; 30s Wingate test protocol (MP; PP; Total Work); Time trial performance 100 kcal		mg inhaled	Terbutalina		
				PP increase by 2.2 ± 0.8 % with Terbutalina		Increase
				MP increase by 3.3 ± 1.0 % with Terbutalina		Increase
				Total Work = 21.9 ± 0.7 kJ	Total Work = 21.2 ± 0.7 kJ	Increase
				TT = 293 ± 15 s	TT = 286 ± 14 s	No changes
Kalsen et al., (19) 2014	Time trial performance 300 kcal	9	Terbutaline 15 mg inhaled	TT = 1.072 ± 145 s	TT = 1.054 ± 125 s	No changes
Kalsen et al., (11) 2016	30 s cycle ergometer sprint (MP; PP; EP); Maximal Voluntary Contraction of m. quadriceps	13	Formoterol 54 µg inhaled	MP was 4.6 ± 0.8 % higher with Formoterol		Increase
				PP was 3.9 ± 1.1 % higher with Formoterol		Increase
				EP was 9.5 ± 3.2 % higher with Formoterol		Increase
				MVC before the sprint was 3.0 ± 0.9 % higher with Formoterol		Increase
				MVC after the sprint was 9.9 ± 0.9 % higher with Formoterol		Increase

PP = peak power; **MP** = mean power; **TPP** = time to peak power; **FI** = fatigue index; **MVC** = maximal voluntary isometric contraction; **MIMS** = maximal isokinetic muscle strength; **HR** = heart rate; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **Ve** = expiratory volume; **MSNA** = muscle sympathetic nerve activity; **vmax** = maximal velocity; **Fmax** = maximal force; **Pmax** = maximal power output; **vopt** = optimal velocity; **Fopt** = optimal force; **vmean** = mean velocity; **vmax/τ** = inicial acceleration; **TTE** = time to exhaustion; **RM** = repetition maximum; **TT** = Time Trial; **EP** = end power

3.4.3 Inhaled ß2-agonists

3.4.3.1 Formoterol

Two studies (4,11) involving 36 participants addressed the effects of inhaled formoterol.

The effect estimates for mean, peak and end power output during a 30 s cycle ergometer sprint and for maximal voluntary contraction of muscle quadriceps were positive, that is, formoterol improved this outcome. (11)

The effect estimates for running time to exhaustion at -20°C at 107% VO_2max were negative for formoterol (not statistically significant). (4)

3.4.3.2 Salbutamol

Eight studies (9,10,12–14,16–18) involving 198 participants addressed the effects of inhaled salbutamol.

A statistically significant effect was detected for quadriceps fatigue test [concentric peak torque (Nm/s)] (14) and for mean power; oxygen consumption (VO_2max) and cycling economy on a 10 km time trial on a cycle ergometer (18).

The effect estimates for mean power and duration of 20 km time trial (12); quadriceps muscle strength during maximal voluntary contraction and femoral nerve magnetic stimulation before and after (i) a maximal incremental cycling test and (ii) 50 maximal isometric one-leg extensions (13); mean power during a 10 km time trial on a cycle ergometer (16); duration of a 3 km time trial, vertical jump height, 1 repetition maximum bench and leg press, peak torque knee flexion and extension (17); mean duration of a 10 km cycling time trial (10) and mean power output during a 10 km time trial (9) were all negative for inhaled salbutamol; none of the effects were statistically significant.

3.4.3.3 Salbutamol + Salmeterol + Formoterol

One study (15) involving 17 participants addressed the effects of the combined inhalation of salbutamol with salmeterol and formoterol.

A statistically significant effect was found for maximal voluntary isometric contraction of muscle quadriceps and for swim ergometer sprint time, but not on the exhaustive swim test. (15)

3.4.3.4 Terbutaline

Two studies (8,19) involving 18 participants addressed the effects of inhaled terbutaline.

A statistically significant effect was detected for maximal voluntary isometric contraction of muscle quadriceps, peak power, mean power and total work during a 30 s Wingate test protocol (8), but not for the time trial performance 100 kcal (8) and 300 kcal (19).

3.4.4 Systemic ß2-agonists

3.4.4.1 Salbutamol

Three studies (20–22) involving 55 participants addressed the effects of oral (20,21) and IV salbutamol (22).

A statistically significant effect was detected on peak power, mean power, force (peak power), time to peak power during a 30 s Wingate test protocol for oral salbutamol, but not for velocity (peak power) and fatigue index. (21)

The effect estimates for maximal isokinetic muscle strength, diastolic blood pressure, $P_{ET}CO_2$ and muscle sympathetic nerve activity were all negative for salbutamol IV 10 µg/min; none of the effects were statistically significant. However, for the same dose and drug, a statistically significant effect was detected on heart rate, systolic blood pressure, pulse pressure and expiratory volume.

On the same study, for salbutamol IV 20 µg/min, a statistically significant effect was detected on heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, expiratory volume, but not for maximal isokinetic muscle strength and $P_{ET}CO_2$. (22)

The effect estimates for mean power and fatigue index during a 30 s Wingate test protocol, maximal voluntary isometric contraction of muscle quadriceps, isometric endurance (time to exhaustion during isometric contraction of muscle deltoideus) and time to exhaustion during an exercise performance at 110% of VO_2max were all negative for oral salbutamol on an acute administration and after 2 weeks administration; none of the effects were statistically significant. However, a statistically significant effect was found for peak power on the first bout during a 30s Wingate test protocol when considering the acute administration of oral salbutamol and during the first 2 of 3 bouts during a 30 s Wingate test protocol when considering the 2 weeks administration of oral salbutamol. (20)

3.4.4.2 Terbutaline

One study (23) involving 7 participants addressed the effects of oral terbutaline.

The effect estimates for force-velocity exercise test (vmax; Pmax; vopt; Fopt); running sprint (vmax; vmean; vmax/τ) and maximal endurance cycling test (peak O_2 uptake; peak ventilation; time to exhaustion) were all negative for oral terbutaline; none of the effects were statistically significant. However, a statistically significant effect was found for the Fmax on the force-velocity exercise test. (23)

3.4.5 Duration of the intervention

3.4.5.1 Single (once)

Fifteen studies (4,8–16,18,19,21–23) involving 295 participants addressed the effects of ß2-agonists on a single administration.

For a single administration, a statistically significant effect was detected on peak power, mean power, force (peak power), time to peak power during a 30 s Wingate test protocol for

oral salbutamol (21); on heart rate, systolic blood pressure, pulse pressure and expiratory volume for salbutamol IV 10 µg/min and on heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, expiratory volume for salbutamol IV 20 µg/min (22); on Fmax on the force-velocity exercise test for oral terbutaline (23); on quadriceps fatigue test [concentric peak torque (Nm/s)] for inhaled salbutamol (14); on maximal voluntary isometric contraction of muscle quadriceps and on swim ergometer sprint time for a combined inhalation of salbutamol with salmeterol and formoterol (15); on mean power, oxygen consumption (VO_2max) and cycling economy on a 10 km time trial on a cycle ergometer for inhaled salbutamol (18); on maximal voluntary isometric contraction of muscle quadriceps, peak power, mean power and total work during a 30s Wingate test protocol for inhaled terbutaline (8) and on mean, peak and end power output during a 30s cycle ergometer sprint and for maximal voluntary contraction of muscle quadriceps for inhaled formoterol (11).

In contrast, and still for a single administration, the effect estimates for running time to exhaustion at -20°C at 107% VO_2max for formoterol (4); for velocity (peak power) and fatigue index for oral salbutamol (21); for mean power and duration of 20 km time trial for inhaled salbutamol (12); for quadriceps muscle strength during maximal voluntary contraction and femoral nerve magnetic stimulation before and after (i) a maximal incremental cycling test and (ii) 50 maximal isometric one-leg extensions for inhaled salbutamol (13); for maximal isokinetic muscle strength, diastolic blood pressure, $P_{ET}CO_2$ and muscle sympathetic nerve activity for salbutamol IV 10 µg/min and for maximal isokinetic muscle strength and $P_{ET}CO_2$ for salbutamol IV 20 µg/min (22); for force-velocity exercise test (vmax; Pmax; vopt; Fopt); running sprint (vmax; vmean; vmax/τ) and maximal endurance cycling test (peak O_2 uptake; peak ventilation; time to exhaustion) for oral terbutaline (23); for exhaustive swim test for a combined inhalation of salbutamol with salmeterol and formoterol (15); for mean power during a 10 km time trial on a cycle ergometer for inhaled salbutamol (16); for the time trial performance 100 kcal for inhaled terbutaline (8); for the time trial performance 300 kcal for inhaled terbutaline (19); for mean power output during a 10 km time trial for inhaled salbutamol (9) and for mean duration of a 10 km cycling time trial for inhaled salbutamol (10) were all negative; none of the effects were statistically significant.

3.4.5.2 Short term (1 week to ≤6 weeks)

One study (20) involving 20 participants addressed the effects of oral salbutamol after 2 weeks administration.

The effect estimates for mean power and fatigue index during a 30 s Wingate test protocol, maximal voluntary isometric contraction of muscle quadriceps, isometric endurance (time to exhaustion during isometric contraction of muscle deltoideus) and time to exhaustion during an exercise performance at 110% of VO_2max were all negative for oral salbutamol after 2 weeks administration; none of the effects were statistically significant. However, a statistically significant effect was found for peak power during 2 of 3 bouts during a 30 s Wingate test protocol. (20)

3.4.5.3 Long term (> 6 weeks)

One study (17) involving 16 participants addressed the effects of inhaled salbutamol during 6 weeks administration.

The effect estimates for peak oxygen consumption, duration of 3 km time trial, vertical jump height, 1 repetition maximum bench and leg press, peak torque knee flexion and extension were all negative for inhaled salbutamol during 6 weeks administration; none of the effects were statistically significant. (17)

4. Discussion

4.1 Main Findings

When comparing the results for the same ß2-agonists on an athlete and on a non-athlete we can verify that in both cases there are statistically significant effects, but they are more prominent on non-athletes. When testing for formoterol, we observe that on the athletes there are not statistically significant effects. In contrast, when formoterol was tested on non-athletes there were statistically significant effects in all the outcomes studied (30 s cycle ergometer sprint [mean power; peak power; end power] and maximal voluntary contraction of m. quadriceps) (11). However, the dose was higher in these latter individuals (54 µg) than in the athletes (18 µg) (4). When testing oral salbutamol 4 mg on athletes we verify a statistically significant effect only on peak power in the first bout of the 30s Wingate test (20), while on non-athletes there is a statistically significant effect in almost all the studied outcomes (peak power, mean power, force and time to peak power on a 30s Wingate test protocol) (21).

When comparing the inhaled ß2-agonists with the systemic ß2-agonists, we found out that there are statistically significant effects in both administration modes, but these effects vary depending on the ß2-agonist. We could note that terbutaline has more statistically significant effects when administered by inhalation (8,19), than when administered orally (23). However, the doses administrated by inhalation (15 mg) were greater than those administrated orally (8 mg). In contrast, we verified that inhaled salbutamol (9,10,12–14,16–18) had less statistically significant effects than oral or intravenous salbutamol (systemic route) (20–22), however the inhaled administrated doses were lower than the systemic administrated doses.

We found out, as well, a statistically significant effect when an inhaled combination of salbutamol with salmeterol and formoterol was studied. (15)

Regarding the duration of the administration, we verified no influence on a long-term administration since there are more statistically significant effects on single administrations.

In contrast to our findings, that found out that there are statistically significant effects in both administration modes (inhaled and systemic), depending on the ß2-agonist and its dose, prior systematic reviews by Kinderman (2006) and Pluim (2011) concluded that no ergogenic potential effects were detected for the inhaled ß2-agonists on capacity or strength in healthy athletes. (24,25) Pluim (2006) went further and stated that the evidence base for assessing possible performance-enhancing effects of systemic ß2-agonists is currently weak. (24)

4.2 Strength and Weaknesses

The strengths of our study are, firstly, the fact that we systematically searched the literature for studies examining the effect of either inhaled or systemic ß2-agonists, resulting in a wider database, so there is a high likelihood that we identified all relevant studies. Secondly, the application of systematic strategies to reduce bias by an assessment of the internal validity of

the included studies. There were low risks of bias in the studies on inhaled and on systemic β2-agonists.

The weaknesses of this review are the fact that none of the included studies examined the effect of β2-agonists during actual performance, so the extrapolation of our findings to actual sports' performance should be done with caution. Moreover, blinding was likely to be insufficient in some studies, because side effects were reported when using the drugs but not placebo. Some data were difficult to use, as they were presented as diagrams and baseline values were lacking. Few studies have tested doses of β2-agonists above the doses allowed by WADA and in the majority of studies the number of subjects tested was reduced.

However, only with a meta-analysis would it be possible to indicate if there are actually effects on the performance induced by the β2-agonists.

5. Conclusion

We did not find any statistically significant performance effects regarding ß2-agonists used at the permitted doses, which in contrast with the studies that included ß2-agonists nowadays forbidden by the "Prohibited List of the World Anti-Doping Agency (WADA) 2019". Therefore, we could conclude that this list should be continuously updated as it has been done lately. More studies about these and other drugs that could potentialize the athletic performance should be done, involving a greater number of participants, athletes and non-athletes and higher doses, always with the purpose of reducing the attempts of having a greater performance with substances and not through practice nor the athlete's physical abilities.

We believe that it would be very useful in the future to make other studies of this kind during competition instead of being made on laboratory due to the fact that the athlete doesn't perform the same way in both contexts.

Another type of study that we think is also needed is the comparison between the same dose of the same ß2-agonist in non-athletes and athletes.

6. Attachments

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1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Beta-2 adrenergic agonists and physical performance

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01/10/2018

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Olga Lourenço

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11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Beatriz Mónico. FCS - UBI Faculty of Health Sciences

Miss Ana Cardoso. FCS - UBI Faculty of Health Sciences

Miss Ana Vilaça. FCS - UBI Faculty of Health Sciences

Assistant/Associate Professor Jorge Gama. CMA – UBI Centre of Mathematics and Applications, University of Beira Interior

Professor Olga Lourenço. CICS - UBI Health Sciences Research Centre

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

FEDER funds through the POCI - COMPETE 2020 - Operational Programme Competitiveness and Internationalisation in Axis I - Strengthening research, technological development and innovation (Project POCI-01-0145-FEDER-007491) and National Funds by FCT - Foundation for Science and Technology (Project UID/Multi /00709/2013)

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Do beta-2 adrenergic agonists increase the physical performance in non-asthmatic healthy individuals?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

We will search the following databases: PubMed, ScienceDirect, Scopus, and ISI Web of Knowledge.
These databases will be searched from inception to 31st December 2018.
The search strategy will include:

PubMed: "adrenergic beta agonists" AND ("athletic performance" OR Doping OR "Physical endurance" OR "muscle strenght")
ScienceDirect: "beta agonists" AND ("athletic performance" OR Doping OR "Physical endurance" OR "muscle strenght")
Scopus: TS=((beta agonists) AND ("athletic performance" OR Doping OR "Physical endurance" OR "muscle strenght"))
ISI Web of Knowledge: TS=((beta agonists) AND ("athletic performance" OR Doping OR "Physical endurance" OR "muscle strenght"))
The search will not be restricted in terms of following language.
We will exclude studies performed in animals, in vitro studies, studies performed in children or adolecents and studies performed in non-healthy populations.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.

Do NOT provide links to your search results.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Doping in sport is a widespread problem not just among elite athletes, but even more so in recreational sport. Beta2-agonists are targets for doping in sport, because of their bronchodilator, anabolic and anti-inflammatory actions.
Most athletes use beta2-agonists to alleviate their asthma or exercise-induced asthma (EIA). However, it was noted that since 1984, the percentage of athletes using inhaled beta2-agonists at the Olympic Games has slightly risen. The question

of whether this is a real increase because of EIA or a misuse by non-asthmatic athletes because of potential ergogenic effects remains open. The increase in the use of inhaled beta2-agonists has led to more stringent anti-doping rules regarding these substances; and since 2001, asthmatic athletes must provide clinical evidence of reversible airway obstruction or bronchial responsiveness in order to use beta2-agonists legitimately.
The starting point of these rules can be traced back to 1972 when inhaled salbutamol was prohibited for the first time at the Olympic Games. Since then, inhaled β2-agonists have alternately been allowed and prohibited. Currently, salbutamol is one of the medications most frequently used by Olympic athletes.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include studies with healthy subjects (adults, male and female); elite athletes, recreational athletes and non-athletic people.
The studies should document the level and intensity of sports participation, the training level (maximal oxygen consumption [VO_2máx]) and the type of sport at inclusion. Athletes will be considered to be highly trained if they have a VO_2máx above 55 mL/kg/min (females) or 60 mL/kg/min (males).
Studies that include some or all participants with any disease, as well as studies in which participants used other medication (except oral contraception in women) will be excluded.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

We will include any intervention with short- or long-acting inhaled or systemic (oral or intravenous) beta2-adrenergic-agonists.
We will exclude studies that include clenbuterol, because this drug was defined as an anabolic agent and not a β_2-agonist by the WADA.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

We will compare beta2-adrenergic agonist use against placebo or no drug.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

We will include all randomized controlled studies that studied the effect of beta2-adrenergic agonists on physical performance.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

The use of the beta2-agonists could be single (once) or administered at multiple occasions.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

. VO_2máx in L/min or mL/Kg/min determined with a maximal exercise test on a treadmill or cycle ergometer.
. Endurance time(s) to exhaustion during an exercise test at a predetermined percentage of VO_2máx.
. Duration time(s) of a time trial; cycling economy (W/L of O_2), in which a certain distance has to be covered or a certain amount of work has to be delivered.
. Peak power (W or W/kg); mean power (W); force (N or N/kg); velocity (rpm); time to peak power (s) and fatigue index (%) during a Wingate test.
. Maximal voluntary isometric contraction of muscles (N); the one-repetition maximum (1RM, kg) or concentric peak torque (Nm/s or Nm/kg/s) during an isokinetic strength test of any muscle group.
. Agility (S); Loughborough soccer passing test (S); Vertical Jump (cm); Loughborough soccer dribbling test (S); Fastest 0-10m (S); FI% 0-10m; Fastest 0-30m (S); FI% 0-30m; Distance (m); VO_2máx on sport-specific field tests.

Timing and effect measures
Primary outcome measurements should be performed prior and at least once after completion of the treatment.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None.

Timing and effect measures

26. * Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Titles and abstracts of studies retrieved using the search strategy will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria. The full text of these potentially eligible studies will be retrieved and independently assessed by two review authors. Discrepancies will be resolved by discussion with the involvement of a third review author if needed. Extraction information will include article references (first author, corresponding author, date, source and language); study characteristics, participant characteristics, sample (size, age, sex, respiratory disease identification and severity), water treatment description; outcomes measured. Two review authors will extract data independently, identify and resolve the discrepancies found through discussion (with a third review author if necessary). Where necessary, authors of eligible studies will be contacted to provide missing or additional data.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

The risk of bias of each study will be independently assessed by two reviewers using the methodological criteria "Cochrane collaboration's tool for assessing risk of bias"

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

All data will be extracted individually by two reviewers onto a specific data extraction sheet, prepared with Excel software. Any discrepancy will be resolved by discussion with the third reviewer.
A descriptive summary with data tables will be produced, in order to summarize literature findings, and if deemed relevant and statistically adequate, meta-analysis using the random effects modeling will be carried out. A narrative synthesis of the data will also be performed, aggregating results by outcome.
A quantitative analysis will be used if the included studies are sufficiently homogenous.
The PRISMA checklist will be followed for reporting of the systematic review.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

If the necessary data are available, subgroup analysis by drug, age group and training level will be performed.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness	No

Diagnostic	No
Epidemiologic	No
Individual patient data (IPD) meta-analysis	No
Intervention	No
Meta-analysis	Yes
Methodology	No
Narrative synthesis	Yes
Network meta-analysis	No
Pre-clinical	No
Prevention	No
Prognostic	No
Prospective meta-analysis (PMA)	No
Review of reviews	No
Service delivery	No
Synthesis of qualitative studies	No
Systematic review	Yes
Other	No

Health area of the review

Alcohol/substance misuse/abuse	Yes
Blood and immune system	No
Cancer	No
Cardiovascular	No
Care of the elderly	No
Child health	No
Complementary therapies	No
Crime and justice	No
Dental	No
Digestive system	No
Ear, nose and throat	No

Education	No
Endocrine and metabolic disorders	No
Eye disorders	No
General interest	No
Genetics	No
Health inequalities/health equity	No
Infections and infestations	No
International development	No
Mental health and behavioural conditions	No
Musculoskeletal	No
Neurological	No
Nursing	No
Obstetrics and gynaecology	No
Oral health	No
Palliative care	No
Perioperative care	No
Physiotherapy	No
Pregnancy and childbirth	No
Public health (including social determinants of health)	No
Rehabilitation	No
Respiratory disorders	Yes
Service delivery	No
Skin disorders	No
Social care	No
Surgery	No
Tropical Medicine	No
Urological	No
Wounds, injuries and accidents	No
Violence and abuse	No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Portugal

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

No I do not make this file publicly available until the review is complete

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

A paper will be submitted to a leading journal in this field.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

beta2-agonists; performance; doping

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

Previous reviews by other authors were published in 2007 and 2011, but questions remain as is apparent by the WADA constant alterations.

Kinderman W. Do Inhaled beta2-agonists have an ergogenic potential in non-asthmatic competitive athletes? Sports Med. 2007; 37: 95-102.

Pluim BM, Hon O, Staal JB et al. Beta2-agonsits and Physical Performance - A systematic review and meta-analysis of randomized controlled trials. Sports Med. 2011; 41: 39-57.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

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